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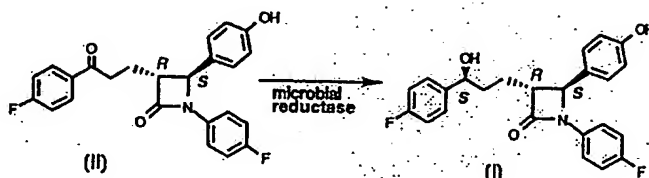
WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : C12P 17/10, C07D 205/08	A1	(11) International Publication Number: WO 00/60107 (43) International Publication Date: 12 October 2000 (12.10.00)
(21) International Application Number: PCT/US99/07445 (22) International Filing Date: 5 April 1999 (05.04.99) (71) Applicant (for all designated States except US): SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HOMANN, Michael, J. [US/US]; 47 Quarry Ridge Road, Clinton, NJ 08809 (US). PREVITE, Edward [US/US]; 655A Cranbury Cross Road, North Brunswick, NJ 08902 (US). (74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published With international search report.

(54) Title: STEREOSELECTIVE MICROBIAL REDUCTION FOR THE PREPARATION OF 1 - (4-FLUOROPHENYL) - 3(R)-[3(S) - HYDROXY-3 - (4-FLUOROPHENYL) PROPYL]-4(S) - (4-HYDROXYPHENYL)-2-AZETIDINONE



(57) Abstract

A process for the stereoselective microbial reduction of compound of formula (II) to compound of formula (I) comprising adding compound of formula (II) to a medium, medium and buffer, medium and solvent, or medium and a mixture of buffer and solvent containing a microorganism, preferably *Rhodococcus fascians* ATCC No.202210 or fungal isolate *Geotrichum candidum* ATCC No. 74487, incubating the resulting mixture, and isolating a hydroxy compound of formula (I), is described. The compound of formula (I) is a serum cholesterol lowering agent.

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10 **STEREOSELECTIVE MICROBIAL REDUCTION FOR THE  
PREPARATION OF 1-(4-FLUOROPHENYL)-3(R) -[3(S)-  
HYDROXY-3-(4-FLUOROPHENYL)PROPYL]-4(S)-(4-  
HYDROXYPHENYL)-2-AZETIDINONE**

15 **BACKGROUND OF THE INVENTION**

1-(4-Fluorophenyl)-3(R) -[3(S)-hydroxy-3-(4-fluorophenyl)-  
propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone is disclosed as a  
cholesterol lowering agent in WO 95/08532, published March 30, 1995.  
U.S. Patent 5,618,707 discloses stereoselective microbial reduction of a  
20 keto intermediate (4-(4-fluoro-benzoyl)butyric acid or a  
phenyloxazolidinone conjugate thereof) used in the preparation of the  
azetidinone to the corresponding hydroxy intermediate using the  
microorganism *Zygosaccharomyces bailii* or *Schizosaccharomyces*  
*octosporus*.

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**SUMMARY OF THE INVENTION**

The present invention relates to a process for the microbiological  
reduction of carbonyl groups which comprises the use of  
microorganisms (obtained from environmental sources and culture  
30 collections, e.g., the American Type Culture Collection (ATCC)) in  
medium, medium and buffer, medium and solvent, or medium and a  
mixture of buffer and solvent to which a ketone compound can be added  
so that a compound having a hydroxy group of desired stereochemistry  
can be formed, accumulated and isolated.

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In particular, the present invention relates to a process for the  
stereoselective reduction of 1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluoro-  
phenyl)propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone to 1-(4-fluoro-

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phenyl)-3(R) -[3(S)-hydroxy-3-(4-fluorophenyl)-propyl]-4(S)-(4-hydroxy-phenyl)-2-azetidinone comprising adding 1-(4-fluoro-phenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)-propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone to a microorganism in medium, medium and buffer, medium and solvent, or  
5 medium and a mixture of buffer and solvent, incubating the resulting mixture, and isolating 1-(4-fluoro-phenyl)-3(R) -[3(S)-hydroxy-3-(4-fluorophenyl)-propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone.

Microorganisms selected from the group consisting of the following genera have been found to be useful in the reduction of this  
10 invention: *Aspergillus*, *Curvularia*, *Doratomyces*, *Geotrichum*, *Mortierella*, *Mucor*, *Saccharomyces*, *Scytalidium*, *Pichia*, *Torulaspora*, *Neurospora* and *Rhodococcus*. The following species of the above genera are preferred: *Aspergillus niveus*, *Curvularia lunata*,  
15 *Doratomyces stemonitis*, *Geotrichum candidum*, *Mortierella isabellina*, *Mucor racemosus* and *circinelloides*, *Saccharomyces cerevisiae* and *uvarum*, *Scytalidium lignicola*, *Pichia methanolitica*, *Torulaspora fermentati* and species, *Neurospora crassa* and *Rhodococcus erythropolis*, *fascians*, *rhodochrous* and species.

In particular, the present invention relates to a process for the  
20 microbiological reduction of the carbonyl group of 1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone (Formula II, below) comprising adding said compound to a microorganism in medium, medium and buffer, medium and solvent, or medium and a mixture of buffer and solvent, especially wherein the  
25 microorganism is *Rhodococcus fascians* ATCC No. 202210 or fungal isolate *Geotrichum candidum* ATCC No. 74487, incubating the resulting mixture, and isolating 1-(4-fluorophenyl)-3(R)-[3(S)-hydroxy-3-(4-fluorophenyl)-propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone (Formula I, below).

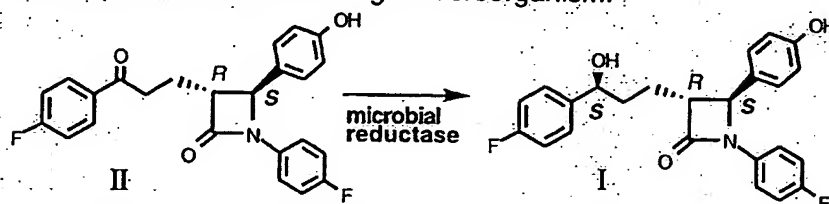
30 Viable cultures of the microorganism and the fungal isolate have been deposited in the collection of the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, where the microorganism has been assigned accession number ATCC 202210 and fungal isolate has been assigned accession number ATCC  
35 74487. Should a deposited culture become lost, destroyed or non-

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viable during the longer of the thirty (30) year period from the date the culture was deposited or the five (5) year period after the last request for the deposited culture or the effective life of the patent which issues from this application, the culture will be replaced, upon notice, by applicants or assignee(s) of this application. Subcultures of *Rhodococcus fascians* ATCC No. 202210 and *Geotrichum candidum* ATCC 74487 are available during the pendency of this application to one determined by the Commissioner of Patents and Trademarks to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. 122 and will be available to the public without restriction once a patent based on this application is granted. Use of the microorganism and fungal isolate is dependent on the US Patent Laws.

#### DETAILED DESCRIPTION

This invention relates to a method for performing the following stereospecific reduction using a microorganism.



The microbiological reduction is carried out by adding the ketone substrate of formula II, above, to medium, medium and buffer, medium and solvent, or medium and a mixture of buffer and solvent containing microorganisms. The incubation may be conducted at temperatures in the range from between about 20°C and about 40°C, preferably 30°C, while adjusting the initial pH value of the reaction in the range from between about 5.0 and about 9.0, preferably 7.0.

The initial concentration of compound II in the reaction may vary from between about 0.5 g/l and about 10.0 g/l, and is preferably 2-4.0 g/l.

Suitable fermentation media, buffers and solvents are known to those skilled in the art. Fermentation media typically contain a carbon and nitrogen source or mixtures thereof, using such ingredients as yeast extract, nutrient broth, dextrose (cerelose), white potato dextrin, soy flour, peptone and other components known in the art. Typical buffers are

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phosphate buffer (e.g., 0.1 M at pH 7), MES (2-[N-morpholino]ethanesulfonic acid), Bis-Tris (bis[2-hydroxyethyl]iminotris[hydroxymethyl]methane), PIPES (1,4-piperazine-diethanesulfonic acid), HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), TRIS (tris(hydroxymethyl)aminomethane) and MOPS (3-[N-morpholino]propanesulfonic acid) buffer (e.g., 0.1 M at pH 7). Typical solvents are acetonitrile, acetone, ethyl ether, isopropanol, t-butanol, isoamyl alcohol, p-dioxane, isopropyl ether, dimethyl sulfoxide, t-butyl methyl ether (TBME), toluene, tetrahydrofuran and  $\text{CH}_2\text{Cl}_2$ . Preferably, the microbial reduction is carried out in fermentation media.

The duration of the chiral reduction reaction may vary from about 18 to about 96 hours, and is preferably about 48-72 hours.

At the end of the reduction reaction, the hydroxy compound of formula I may be extracted by well known methods, using organic solvents such as ethyl acetate (EtOAc), t-butyl methyl ether (TBME), methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) and the like. Adsorption to resins, chromatography, and other physical methods known to the art may also be used to extract the hydroxy compound of formula I.

A large number of microorganisms were investigated to determine whether or not they reduce the ketone compound of formula II. Many such microorganisms failed to provide the desired specificity or productivity.

The examples below demonstrate the evaluation of microorganisms in the reduction of this invention and the preparation of milligram quantities of the hydroxy compound of formula I.

#### Example 1

The general method for identifying the stereoselective microbial reduction of the compound of formula II for use as a synthetic precursor for the production of the compound of formula I is described below.

Seed cultures of yeast, filamentous fungi, and bacteria were grown in 125 ml or 300 ml flasks containing 25 ml or 50 ml of YPD (1% yeast extract, 2% peptone, 2% dextrose; pH 5.5), SIM6 (3.5% soy flour, 5% white potato dextrin, 0.5% cerelose, 2 mg/l cobalt chloride, 0.5% calcium carbonate; pH 6.0) and NYC (0.8% nutrient broth, 2% yeast extract, 1.1% cerelose; pH 7.0) media, respectively, for 72 hours at 30°C with agitation (175-250 rpm) prior to inoculation (4 % v/v) into flask

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- fermentations (25ml YPD/125 ml flask for yeast and filamentous fungi or 25ml NYC /125 ml flask for bacteria) which were incubated at 30°C with agitation (250 rpm). In all fermentations, medium pH was adjusted prior to inoculation but was not controlled during culture propagation and
- 5 ketone reduction. Reduction was initiated by adding 0.5-1.0 g/l of the ketone compound of formula II dissolved in ethanol (25 mg/ml) directly to cultures following 24 hours of growth. Samples of fermentation broth extracted with EtOAc (1:1) following 48 hours incubation with substrate were analyzed by reverse-phase HPLC. Cultures demonstrating
- 10 consistent reduction activity without significant substrate degradation following repeated fermentations using this procedure were further analyzed by chiral HPLC to determine the configuration of the product alcohol. Cultures capable of reducing the ketone of formula II at 1.0 g/l in high enantiomeric excess yielding the hydroxy compound of formula I
- 15 (the *S* enantiomer), are summarized in Table 1.

**Table 1.** Microorganisms capable of selectively reducing Compound II to Compound I at 1.0 g/l.

Culture	Strain #	% EE, <i>S/R</i>	% Yield
<i>Aspergillus niveus</i>	12276	100 <i>S</i>	7
<i>Curvularia lunata</i>	34477	100 <i>S</i>	18
<i>Mucor racemosus</i>	7924	100 <i>S</i>	4
<i>Mucor circinelloides</i>	1207a	100 <i>S</i>	9
<i>Saccharomyces cerevisiae</i>	Y-2034	100 <i>S</i>	8
<i>Saccharomyces uvarum</i>	10613	100 <i>S</i>	11
	32634	100 <i>S</i>	7
<i>Pichia methanolitica</i>	58403	84 <i>S</i>	24
<i>Torulaspora fermentati</i>	20100	100 <i>S</i>	5
<i>Torulaspora species</i>	66815	100 <i>S</i>	14
<i>Neurospora crassa</i>	14692	76 <i>S</i>	4
<i>Rhodococcus erythropolis</i>	25544	100 <i>S</i>	6
<i>Rhodococcus fascians</i>	202210	100 <i>S</i>	46
<i>Rhodococcus rhodochrous</i>	999	100 <i>S</i>	12
	21243	100 <i>S</i>	12
	29670	100 <i>S</i>	13
	29675	100 <i>S</i>	8

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**Table 2.** Effect of bioconversion parameters on productivity of *R. fascians* ATTC No. 202210.

Seed Propagation conditions: 30°C, 250 rpm	Bioconversion Conditions (25 ml media/125 ml flask, 250 rpm)	% Yield
25 ml NYC /125 ml flask 24 hours (4% v/v transfer)	1 g/l : YPD, 30°C	41
	2 g/l: YPD, 30°C	32
25 ml YPD /125 ml flask 24 hours (4% v/v transfer)	1 g/l: YPD, 30°C	50
	2 g/l: YPD, 30°C	42
25 ml NYC /125 ml flask 72 hours (4% v/v transfer)	1 g/l: NYC, 25°C	45
	1 g/l: NYC, 30°C	42
	1 g/l: YPD, 30°C	47
	1 g/l: NYC, 35°C	48
	2 g/l: NYC, 25°C	44
	2 g/l: NYC, 30°C	43
	2 g/l: YPD, 30°C	44
	2 g/l: NYC, 35°C	39
25 ml TGP /125 ml flask 24 hours (4% v/v transfer)	1 g/l: TGP, 30°C	69
	2 g/l: TGP, 30°C	64
	4 g/l: TGP, 30°C	28
	10 g/l: TGP, 30°C	11
25 ml TGP /125 ml flask 24 hours (4% v/v transfer)	4 g/l: 5X cell concentrate, TGP, 30°C	68
	10 g/l: 5X cell concentrate, TGP, 30°C	31

Ketone compound of formula II dissolved in ethanol (25-50 mg/ml) added at 1-10 g/l where indicated following 24 hours of growth.

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**Table 3.** Effect of bioconversion parameters on productivity of *G. candidum* ATCC No. 74487.

Seed Propagation conditions	Bioconversion Conditions (25 ml media/125 ml flask)	% Yield
25 ml SIM-6 /125 ml flask, 30°C, 250 rpm 72 hours (4% v/v transfer)	2 g/l: TGP, 30°C	18
	4 g/l: TGP, 30°C	9
	10 g/l: TGP, 30°C	6
	2 g/l: YPD, 30°C	33
	2 g/l: YPD, 35°C	39
	2 g/l: TNC, 30°C	38
	2 g/l: TNC, 35°C	45
	2 g/l: TN2C, 30°C	54
	2 g/l: TN2C, 35°C	46

Ketone compound of formula II dissolved in DMSO (25-50 mg/ml) added at 2-10 g/l following 24-48 hours of growth. TNC medium: 1% Tastone 154, 2% NZ-amine, 3% cerelose, pH 5.5. TN2C medium: TNC medium with 6% cerelose.

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### Example 3

Milligram quantities of the hydroxy compound of formula I derived from the stereoselective reduction of ketone compound of formula II were prepared using *Rhodococcus fascians* ATCC No. 202210 and fungal isolate *Geotrichum candidum* ATCC No. 74487 in multiple flask fermentations employing conditions summarized in Tables 2 and 3. Following 72-96 hours of incubation, fermentation broths of each of the cultures were pooled prior to centrifugation to isolate the cells which harbor most of the product and residual substrate. The cell pellets were extracted with TBME (10-20 volumes/wet weight). Anhydrous  $MgSO_4$  was added to the TBME extract to remove residual water, the extract was filtered and the filtrate concentrated by evaporation.

Extract concentrate was subjected to purification by preparative thin layer chromatography employing 10-20 GF silica plates (20cm X 20cm X 1000 micron) and developed with a solution of EtOAc:hexane (50:50). Material comigrating with the desired product was scraped from each of the silica plates, pooled and eluted from the silica with TBME which was subsequently evaporated to dryness. Approximately 170 mg of product derived from 450-600 mg of ketone compound of formula II was isolated from each culture bioconversion. Isolated material was confirmed to be the desired hydroxy compound of formula I by reverse phase and chiral HPLC, NMR, and mass spectrum analyses.

## WHAT IS CLAIMED IS:

1. A process for the stereoselective reduction of 1-(4-fluorophenyl)-  
5 3(R)-[3-oxo-3-(4-fluorophenyl)propyl]-4(S)-(4-hydroxyphenyl)-2-  
azetidinone to 1-(4-fluorophenyl)-3(R)-[3(S)-hydroxy-3-(4-fluorophenyl)-  
propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone comprising adding 1-(4-  
fluoro-phenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)-propyl]-4(S)-(4-  
hydroxyphenyl)-2-azetidinone to a microorganism in medium, medium  
10 and buffer, medium and solvent, or medium and a mixture of buffer and  
solvent, incubating the resulting mixture, and isolating 1-(4-fluoro-  
phenyl)-3(R)-[3(S)-hydroxy-3-(4-fluorophenyl)-propyl]-4(S)-(4-  
hydroxyphenyl)-2-azetidinone.
- 15 2. A process of claim 1 wherein the microorganism is of the genera  
selected from the group consisting of *Aspergillus*, *Curvularia*,  
*Doratomyces*, *Geotrichum*, *Mortierella*, *Mucor*, *Saccharomyces*,  
*Scytalidium*, *Pichia*, *Torulaspora*, *Neurospora* and *Rhodococcus*.
- 20 3. A process of claim 2 wherein the microorganism is of the species  
selected from the group consisting of *Aspergillus niveus*, *Curvularia*  
*lunata*, *Doratomyces stemonitis*, *Geotrichum candidum*, *Mortierella*  
*isabellina*, *Mucor racemosus* and *circinelloides*, *Saccharomyces*  
*cerevisiae* and *uvarum*, *Scytalidium lignicola*, *Pichia methanolitica*,  
25 *Torulaspora fermentati* and *species*, *Neurospora crassa* and  
*Rhodococcus erythropolis*, *fasciens*, *rhodochrous* and *species*.
4. A process of claim 3 wherein the microorganism is *Rhodococcus*  
*fascians* ATCC No. 202210 or fungal isolate *Geotrichum candidum*  
30 ATCC No. 74487.
5. A process of claim 4 wherein the microorganism is  
*Rhodococcus fascians* ATCC No. 202210.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/07445

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C12P17/10 C07D205/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C12P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Section Ch, Week 198632 Derwent Publications Ltd., London, GB; Class B03, AN 1986-208964 XP002123973 & JP 61 141894 A (SANKYO CO LTD), 28 June 1986 (1986-06-28) abstract	1-3
A		4,5
Y	SANTANIELLO E. ET AL.: "The Biocatalytic Approach to the Preparation of Enantiomerically Pure Chiral Building Blocks." CHEM. REV., vol. 92, 1992, pages 1071-1087, XP002123971 the whole document	1-3
A		4,5
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

26 November 1999

Date of mailing of the international search report

15/12/1999

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# INTERNATIONAL SEARCH REPORT

International Application No  
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BELAN A. ET AL.: "Use of Biological Systems for the Preparation of Chiral Molecules." J. ORG. CHEM., vol. 52, 1987, pages 256-260, XP002123972	1-3
A	the whole document	4,5
Y	WO 97 16424 A (SCHERING CORP.) 9 May 1997 (1997-05-09)	1-3
A	page 2 -page 3; claim 1	4,5

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Appl. No.

PCT/US 99/07445

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